Oral amoxicillin-clavulanate for treating diabetic foot infections

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Abstract: AIM To assess amoxicillin-clavulanate (AMC) for the oral therapy of diabetic foot infections (DFIs), especially for diabetic foot osteomyelitis (DFO). METHODS We performed a retrospective cohort analysis among 794 DFI episodes, including 339 DFO cases. RESULTS The median duration of antibiotic therapy after surgical debridement (including partial amputation) was 30 days (DFO, 30 days). Oral AMC was prescribed for a median of 20 days (interquartile range, 12-30 days). The median ratio of oral AMC among the entire antibiotic treatment was 0.9 (interquartile range, 0.7-1.0). After a median follow-up of 3.3 years, 178 DFIs (22%) overall recurred (DFO, 75; 22%). Overall, oral AMC led to 74% remission compared with 79% with other regimens (-test; P = 0.15). In multivariate analyses and stratified subgroup analyses, oral AMC resulted in similar clinical outcomes to other antimicrobial regimens, when used orally from the start, after an initial parenteral therapy, or when prescribed for DFO. CONCLUSIONS Oral AMC is a reasonable option when treating patients with DFIs and DFOs.

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Oral Amoxicillin/Clavulanate for Treating Diabetic Foot Infections

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ABSTRACT

Some clinicians avoid amoxicillin-clavulanate (AMC) for the oral therapy of diabetic foot infections (DFI), especially for osteomyelitis (DFO), due to its poor bioavailability and bone penetration of all antibiotics from the β-lactam class. We performed a retrospective cohort analysis among 794 DFI episodes, including 339 DFO cases. The median duration of antibiotic therapy after surgical debridement (including partial amputation) was 30 days (DFO 30 days). Oral AMC was prescribed for a median of 20 days (interquartile range, 12-30 d). The median ratio of oral AMC among the entire antibiotic treatment was 0.9 (interquartile range, 0.7-1.0). After a median follow-up of 3.3 years, 178 DFIs (22%) overall recurred (DFO 75; 22%). Overall, oral AMC led to 74% remission compared to 79% with other regimens (χ^2-test; p=0.15). In multivariate analyses and stratified subgroup analyses, oral AMC resulted in similar clinical outcomes to other antimicrobial regimens; either when used orally from the start, after an initial parenteral therapy, or when prescribed for DFOs. We conclude that oral AMC is a reasonable option when treating patients with DFIs and DFOs.

Introduction

Many authorities on orthopedic infections avoid oral β-lactam antibiotics for the post-surgical treatment of implant-related orthopedic infections or chronic osteomyelitis[1] because of poor bioavailability and bone penetration concerns[2]. Per analogic consequence, experts argue also often against oral β-lactam agents for diabetic foot infections (DFI), especially when bone (DFO) is involved[1,2], although this avoidance of β-lactams is not ubiquitous. There might be countries or settings lacking this particular concern.

For DFI, there is a great variability in antibiotics used by clinicians, but amoxicillin/clavulanic acid (AMC) is among the most frequently administered oral β-lactam for DFI worldwide[2-4]. Major practice-oriented guidelines, such as those of the Infectious Diseases Society of America (IDSA)[5] and the International Working Group on the Diabetic Foot (IWGDF)[6] suggest that oral AMC works for mild and moderate DFI. However, despite widespread potential implications in daily clinical life, scientific clinical data concerning this particular question are non-existing and the literature needs scientific confirmation regarding the use or avoidance of oral β-lactams, in particular AMC, for DFI. Therefore, we conducted the first large single-center cohort study on this topic.

Methods

The Geneva University Hospitals has been running a clinical pathway for adult DFI patients from March 2013 to March 2018. As a part of a quality assurance program, patients were not required to provide informed consent[7]. Our DFI definitions based on the IDSA guidelines[5] requiring two signs of local inflammation and pathogens in two intraoperative tissue samples. We diagnosed diabetic foot osteomyelitis (DFO) by a combination of clinical features (e.g., visible bone) plus imaging (bone lesions without prior surgery or trauma); and/or microbiological results (bacteria on several intraoperative bone cultures). We excluded major

amputations and only included DFOs if there was residual osteitis after surgery. We defined remission as the absence of clinical, laboratory or imaging evidence of the original infection after a minimum follow-up of two months. Of note, in our region oral AMC covers most DFI pathogens for at least 70%, including anaerobes such as *Bacteroides fragilis*.

Results

We followed 794 first DFI episodes (419 patients; 220 females; median age 69 years) for a median duration of 3.3 years after treatment. A total of 241 patients (57.5%) revealed one DFI episode, 178 had between two and 12 DFI new "first" episodes. During the five-year study period, 74 patients died for reasons other than DFIs after the minimal follow-up time. Their death was unrelated to infection and thus we kept them in the analyses. Fourteen patients (3%) had an immune-suppressive condition other than diabetes (dialysis, cancer, advanced cirrhosis, or medication-related). In 19% of the episodes an antibiotic therapy within the last two weeks influenced the intraoperative cultures. Intraoperative cultures revealed 107 different constellations of microorganisms. The most frequent pathogens were *Staphylococcus aureus* (n=273; of which 61 methicillin-resistant), streptococci (121), and gram-negatives (269). According to the IDSA criteria[5], we revealed oft tissue DFIs were graded upon the with 81 mild soft tissue DFIs, 587 moderate and 126 severe DFIs, while the 339 DFO episodes (43%) mostly occurred in the forefoot with less hindfoot (8%) or ankle (9%) involvement.

Therapy

The median number of surgical debridements per episode was 1 (range, 0-7 surgeries). We debrided all DFOs in the operating theatre; along with partial toe amputations. The median duration of post-surgical systemic antibiotic therapy was 30 days (DFO 30 days), with a median of five days parentally (DFO six days). We used 141 different antibiotic regimens,

with changes during their treatment course. In total, we treated 295 DFI episodes with a single agent, 186 with two, 125 with three, 41 with four and 20 with five antimicrobial agents. The most frequently prescribed drug classes, other than β-lactams, were: quinolones (n=204); glycopeptides (120); clindamycin (84); co-trimoxazole (37); and, rifampicin (14).

Overall, we used β-lactams in 631 DFI episodes (79%) including as intravenous therapy and partial oral therapy. Among the oral β-lactam agents, AMC (500 mg amoxicillin & 125 mg clavulanic acid or 875 mg amoxicillin & 125 clavulanic acid) was the most frequent occurring in 301 cases. We administered it during a median of 20 days (interquartile range, 12-30 d; DFO 22 days); corresponding to a median ratio of 0.9 between AMC among all other oral medications (interquartile range, 0.7-1; ratio in DFO 0.9). In 77 episodes, the entire antibiotic therapy consisted of oral AMC (DFO 26 cases). The daily dosing of AMC were 1000 mg bid, 625 mg tid, or 1000 mg tid, with a median of 2000 mg (interquartile range, 1875-2500 mg including for DFO). Of note, no oral AMC therapy was changed or stopped because of severe adverse events, while small cutaneous mycosis and diarrheas required additional medication in a minority of patients. Finally, in 234 cases (29%) angiologists revascularized the limb, 95 episodes underwent hyperbaric oxygen therapy of 30 sessions each, and we instructed all patients in proper pressure offloading measures.

Outcomes

After a median delay of 7.5 months after the end of therapy, 178 (178/794; 22%) DFI episodes recurred (DFO 75; 22%). Outcomes with oral AMC therapy were not different from other agents overall, including for DFOs (Table 1). Oral AMC led to 74% remission (131/178) compared to 79% (485/616) in non-β-lactam regimens (χ^2-test; p=0.15). The corresponding incidences in the subset of DFO cases were 81% (215/261) versus 80%

(60/75), respectively. In view of the considerable case-mix, we adjusted with a Cox regression analysis (Table 2 left column). We confirmed that oral AMC therapy achieved the same remission, either when administered from the start (hazard ratio 0.9, 95%CI 0.5-1.6), or when calculated as absolute numbers of treatment days (HR 1.0, 95%CI 0.9-1.1). These results were also consistent for the subset of DFOs (Table 2 right column).

Discussion

In our DFI cohort, oral AMC therapy did not influence remission. This finding was irrespective of whether we treated DFOs or soft tissue infections, from the start or after initial parenteral administration, irrespective of alterations of the its standard dosing, when computed as a ratio of the entire course or analyzed as absolute numbers of treatment days; or when compared with non-betalactam agents. Our study strengths are its size and a well-defined cohort of patients with a close follow-up. On the basis of a conservative estimate of 20% failures when treating DFI[2], our 794 DFI episodes (one of the largest databases), yielded the necessary sample size to detect a 7% difference in a superiority design, or a 10% difference in a non-inferiority analysis. A randomized trial designed for detecting smaller differences requires more than thousand patients, which is clinically impracticable.

From a pharmacological point of view, all β-lactams penetrate poorly into bone. *In vitro*, the reported penetrations vary widely, even for the same molecule[8]. For example, the average bone-to-serum ratios vary up to three-fold for amoxicillin and 25-fold for clavulanic acid[8]. Even when administered parenterally, β-lactams may reveal a bone-to-serum ratio as low as 20%[8]. In contrast and clinically speaking, many case series advocate the effectiveness of oral AMC therapy for osteomyelitis, such as jaw or skull base osteomyelitis[9]. To cite further clinical examples, Sayana et al. successfully treated vertebral osteomyelitis with AMC for

eight weeks[10]. Bassey reported an 83% success in 44 post-surgical cases staphylococcal osteomyelitis with only five days of parenteral AMC, followed by six weeks of oral AMC[11]. Bell reported a successful therapy for 19 adult patients with high-dose oral penicillins for staphylococcal osteomyelitis[12]. Hodkin published the remission in 10 of 14 similar patients with chronic staphylococcal osteomyelitis[13]. In the pediatric population, several studies in the 1980'ties supported the effectiveness of oral β-lactam care for acute osteomyelitis[10].

In a study specifically addressing DFIs (including 26 DFO cases), Lipsky et al. performed a randomized multicenter trial on 108 patients comparing two different regimens[14]. Enrollees were allocated into one week of parenteral antibiotic therapy, followed by two weeks of either oral quinolones or oral AMC, at standard doses. The clinical remission risk was 85% versus 83%, respectively, a success rate in line with most published DFI studies[3]. Lazaro-Martinez et al. randomized DFO patients to conservative antibiotic treatment (for 90 days) or surgical resection plus antibiotics for 10 days[15]. In the antibiotic arm, oral agents were given from the start (24 cases with oral AMC 1000 mg bid; 24 cases with other oral antimicrobials). All outcomes were equal. Moreover, several guidelines and practice-oriented expert reviews recommend oral AMC in DFI, at least in mild cases[2-6]. Finally, Senneville et al. found that the only factor predicting success in DFOs would be the susceptibility of the organism to the antibiotic employed. No other factor, including bone antibiotic penetration mattered[16].

In conclusion, we believe that our clinical data, along with the literature and authoritative guidelines[5], suggest that oral AMC is a reasonable option when treating patients with DFIs and DFOs.

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Conflict of interest

KG, DL, EvD, PS, FW, MB, TH and BK declare no conflict of interest. IU and BAL have received research donations from Innocoll Ltd. for another project.

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Table 1 - Characteristics of patients with diabetic foot osteomyelitis without major amputation

	Clinical remission		Clinical failure
n = 339	**n = 264**	***p* value***	**n = 75**
Female sex	78 (30%)	0.16	16 (21%)
Age (median)	70 years	0.08	65 years
Insulin therapy	157 (66%)	0.42	47 (71%)
Bacteremia	26 (11%)	0.42	5 (8%)
First episode of diabetic foot osteomyelitis	135 (51%)	0.34	43 (57%)
Number of past infection episodes (median)	1	0.18	1
Number of surgical interventions (median)	1 (range, 0-2)	0.30	1 (range, 0-6)
Hyperbaric oxygen therapy	31 (12%)	0.71	10 (13%)
Duration of antibiotic treatment (median)	30 days	0.68	31 days
Duration of intravenous antibiotics (median)	6 days	0.37	5 days

Oral co-amoxiclav for the entire course	18 (7%)	0.54	7 (9%)	
Duration of oral co-amoxiclav (median)	21 days	0.32	23 days	
Ratio co-amoxiclav/ oral therapy (median)	0.8	0.50	0.9	
Median dose of oral co-amoxiclav	2000 mg	0.89	2000 mg	
Non co-amoxiclav therapies	215 (81%)	0.78	60 (80%)	
Use of oral rifampicin	17 (6%)	0.64	6 (8%)	
Revascularization	81 (31%)	0.11	16 (21%)	

and italic. Pearson-χ^2 and Wilcoxon-ranksum-tests, as appropriate

Significant *p* values ≤ .05 (two-tailed) are displayed ***in bold***

Table 2 - Univariate and multivariate analyses with the outcome "remission," stratified by osteomyelitis *(cluster-controlled Cox regression; hazard ratios, with 95% confidence intervals)*

n = 794, all episodes			**n = 339, only osteomyelitis**	
Univariate	***Multivariate***	**Variable**	***Univariate***	***Multivariate***
0.7, 0.5-1.1	0.8, 0.7-1.2	Female sex	0.7, 0.4-1.2	n.d.
1.0, 1.0-1.0	n.d.	Age (continuous)	1.0, 1.0-1.0	1.0, 0.9-1.1
1.0, 0.9-1.2	1.1, 0.8-1.5	- Age > 60 years	1.4, 0.9-2.5	n.d.
0.9, 0.5-1.4	n.d.	Immune-suppression*	n.d.	n.d.
1.3, 0.9-1.8	n.d.	Insulin therapy	n.d.	n.d.
1.2, 0.9-1.6	1.4, 0.9-1.9	Bacteremia	0.7, 0.3-1.8	n.d.
1.0, 0.9-1.1	1.0, 0.9-1.1	First episode of infection	1.1, 0.9-1.3	n.d.
1.0, 0.7-1.6	n.d.	More than three past episodes	0.4, 0.2-1.1	n.d.
1.0, 0.9-1.1	1.1, 0.9-1.2	Number of past episodes	0.8, 0.7-1.1	0.8, 0.5-1.2
0.9, 0.8-1.1	1.1, 0.8-1.5	Presence of osteomyelitis	n.d.	n.d.
0.9, 0.6-1.2	1.1, 0.7-1.8	- Calcaneal osteomyelitis	0.9, 0.6-1.2	n.d.

0.9, 0.8-1.1	1.0, 0.8-1.1	Number of surgeries	0.9, 0.7-1.2	0.9, 0.4-1.9
0.7, 0.6-0.9	1.0, 0.7-1.4	- (partial) amputation	n.d.	n.d.
1.0, 1.0-1.0	n.d.	Use of vacuum-assistance	1.0, 0.9-1.1	n.d.
n.d.	n.d.	Use of hyperbaric oxygen	1.9, 0.9-3.8	n.d.
n.d.	n.d.	Use of hyperbaric oxygen therapy	1.2, 0.5-3.2	1.3, 0.7-2.2
1.0, 1.0-1.0	1.0, 0.9-1.1	Duration of total antibiotics	1.0, 1.0-1.0	1.0, 1.0-1.0
1.0, 1.0-1.0	1.0, 0.9-1.1	Duration of parenteral antibiotics	1.0, 1.0-1.0	n.d.
0.8, 0.5-1.1	n.d.	Oral rifampicin	0.9, 0.4-2.1	n.d.
1.2, 1.0-1.5	0.9, 0.5-1.6	Oral co-amoxiclav entirely	2.2, 1.0-4.9	1.5, 0.5-4.7
1.0, 0.9-1.1	1.0, 0.9-1.1	Duration of oral co-amoxiclav use	1.0, 0.9-1.1	1.0, 0.9-1.1
0.4, 0.5-4.3	0.4, 0.1-3.6	Ratio between duration of oral co-amoxiclav/entire oral course	n.d.	n.d.
1.0, 0.9-1.1	1.0, 0.9-1.1	Median dose of co-amoxiclav	1.0, 0.9-1.1	1.0, 0.9-1.1
1.0, 0.7-1.4	1.0, 0.7-1.3	Revascularisation	0.7, 0.4-1.3	n.d.

n.d. = not done

* Immune-suppression beyond that of diabetes mellitus = Active cancer, dialysis, cirrhosis CHILD C, untreated HIV disease and immunosuppressive drugs > equivalent of 15 mg prednisolone par day